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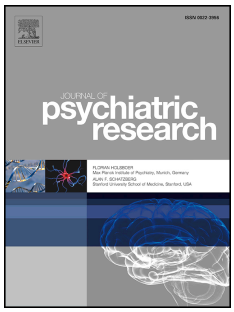

Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies

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Mapping Risk Factors for Depression across the Lifespan: An Umbrella Review of Evidence from Meta-Analyses and Mendelian Randomization Studies

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Abstract

The development of depression may involve a complex interplay of environmental and genetic risk factors. PubMed and PsycInfo databases were searched from inception through August 3, 2017, to identify meta-analyses and Mendelian randomization (MR) studies of environmental risk factors associated with depression. For each eligible meta-analysis, we estimated the summary effect size and its 95% confidence interval (CI) by random-effects modeling, the 95% prediction interval, heterogeneity with I^2, and evidence of small-study effects and excess significance bias. Seventy meta-analytic reviews met the eligibility criteria and provided 134 meta-analyses for associations from 1,283 primary studies. While 109 associations were nominally significant ($P < 0.05$), only 8 met the criteria for convincing evidence and, when limited to prospective studies, convincing evidence was found in 6 (widowhood, physical abuse during childhood, obesity, having 4-5 metabolic risk factors, sexual dysfunction, job strain). In studies in which depression was assessed through a structured diagnostic interview, only associations with widowhood, job strain, and being a Gulf War veteran were supported by convincing evidence. Additionally, 8 MR studies were included and provided no consistent evidence for the causal effects of obesity, smoking, and alcohol consumption. The proportion of variance explained by genetic risk factors was extremely small (0.1-0.4%), which limited the evidence provided by the MR studies. Our findings suggest that despite the large number of putative risk factors investigated in the literature, few associations were supported by robust evidence. The current findings may have clinical and research implications for the early identification of individuals at risk for depression.

Keywords: depression; umbrella review; risk factors; meta-analyses; psychiatry; prevention

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1. Introduction

Major depressive disorder is a leading cause of disability worldwide (Eke et al., 2016) and is associated with psychosocial dysfunction (Birnbaum et al., 2010), increased health care use (Birnbaum et al., 2010), and excess mortality (Walker et al., 2015). Data from the World Mental Health (WMH) Survey indicates that the lifetime prevalence of a major depressive episode significantly varies across countries (Bromet et al., 2011).

Depression is a complex multi-factorial disorder (Otte et al., 2016), and heritability of the broad depression phenotype has been estimated to be approximately 37% (Flint and Kendler, 2014). Several environmental risk factors have been posited to contribute to the development of depression, including but not limited to childhood maltreatment (Li et al., 2016), childhood loss of a parent (Bifulco et al., 1987; Harris et al., 1986), lack of adequate parental care (Bifulco et al., 1987; Harris et al., 1986; Parker et al., 1997), unemployment, lower educational attainment, lower social support, the absence of a partner, lower physical activity (Schuch et al., 2016; Schuch et al., 2018), and cannabis use (Kessler and Bromet, 2013; Lev-Ran et al., 2014; Otte et al., 2016). Emerging evidence also suggests that gene-environment interactions may contribute to the development of depressive episodes (Januar et al., 2015), and accumulating evidence also indicates that epigenetic mechanisms may play a role in the psychopathophysiology of this illness. Although some evidence suggests that the onset of depression can be prevented, the field awaits more conclusive data (Munoz et al., 2010; van Zoonen et al., 2014).

The identification of environmental risk factors, some of which could be potentially modifiable, may be useful toward designing more targeted and effective preventative strategies for depression. Observational studies are used to explore the association of an exposure to an outcome but are frequently affected by residual confounding, undetected bias, or reverse causality, which may generate unreliable associations that are not dependable indicators of causality (Salanti and Ioannidis, 2009). Mendelian randomization (MR) studies may provide a methodologically sound and cost-effective alternative to infer causation while providing an analogy to a randomized controlled trial. In those studies, an instrumental variable (often a genetic risk score) associated with the exposure was employed, and associations between the instrumental variable and outcome (here, depression) are considered to reflect a causal effect of the exposure on the outcome if certain assumptions are met. Since MR studies largely overcome the problems of confounding and reverse causality, they can provide

stronger evidence regarding the causal effect of an environmental risk factor (Gage et al., 2013).

Several systematic reviews and meta-analyses of environmental risk factors for depression have been published. In addition, MR experiments have been increasingly employed in an attempt to elucidate potential risk factors for depression (Gage et al., 2013). Nevertheless, no systematic effort has been made to our knowledge to synthesize the breadth of the evidence from this composite literature. The umbrella review is a systematic review of multiple meta-analyses on a specific research topic (Ioannidis, 2009) that can be used to provide a wider picture of that extensive literature. We therefore performed an umbrella review of meta-analyses and MR studies that investigated environmental risk factors for depression. Finally, we also assessed whether there are hints of various biases in this literature that may undermine the strength or reliability of the evidence. These hints included excess of significance, large heterogeneity, and small-study effects. Therefore, associations supported by the strongest epidemiologic evidence were identified.

2. Materials and methods

2.1. Search strategy and eligibility criteria

An umbrella review was conducted following an a priori defined protocol (available from the authors upon request). We systematically searched the PubMed and PsycInfo databases from inception to August 3, 2017, to identify meta-analyses of observational studies (i.e., cross-sectional, case-control, and prospective) investigating associations of environmental (non-genetic) risk factors for depression. Furthermore, MR studies that examined putative environmental risk factors for depression were also included. This umbrella review focused on major depressive disorder. Therefore, meta-analyses and MR studies that specifically assessed environmental risk factors for perinatal depression were excluded, since this is a specific form of depression with distinct features (American Psychiatric Association, 2013). Detailed search strings are provided in the supplement that accompanies the online version of this article. We included meta-analyses published in English that assessed one or more environmental factors (including other disease conditions) for associations with depression, and that included at least 3 datasets (i.e., component studies) and provided some measure of association. A diagnosis of depression had to be established through validated structured or semi-structured interviews based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), the International

Classification of Diseases (ICD) (World Health Organization, 1993), or other consensus-based diagnostic criteria for depression (e.g. the Research Diagnostic Criteria) (Endicott and Spitzer, 1979). We also considered studies in which case ascertainment for depression was established via a validated screening instrument with a cutoff score (e.g., the Beck Depression Inventory, the Patient Health Questionnaire-9, and the Zung Self-Rating Depression Scale) and a clinician code-based diagnosis based on specific criteria (e.g., ICD). Studies in which the case ascertainment of depression was made solely on clinician diagnosis without a specific diagnostic criteria-based code were deemed ineligible for inclusion in this umbrella review.

2.2. Data extraction

Data extraction was independently conducted by two investigators, and in cases of discrepancies, a consensus was reached through mutual discussion. From each eligible article, we recorded the first author, journal, year of publication, investigated risk factors, and the number of included studies. We also extracted study-specific risk estimates (relative risk [RR], odds ratio [OR], hazard ratio [HR], or incident risk ratio) with their corresponding 95% confidence intervals (CIs) and the number of cases and controls. Whenever the studies included several control groups, we considered associations with the healthy control group. The impact of putative risk factors for depression may differ across the lifespan (Fiske et al., 2009; Maughan et al., 2013). Therefore, we also annotated whether the included meta-analyses primarily synthesized evidence for depression in youths (i.e., pediatric depression, age < 18 years) or in older adults (late-life depression, age ≥ 55 years). When 2 or more meta-analyses were available on the same exposure, we considered the one with the largest number of component datasets. Finally, we extracted data from forest plots of meaningful subgroup analyses from the original reports when at least 3 datasets were included (e.g., analyses limited to prospective studies). For MR studies, we extracted data on the study population, sample size, genetic instruments, the variance of the environmental risk factor explained by the genetic instruments (R^2), and the MR effect estimates (odds ratio, hazard ratio, or regression coefficient β). If R^2 was missing from the study, but other MR studies that used the same genetic variants as instrumental variables provided this parameter, we used the R^2 values provided by those studies.

2.3. Methodological quality assessment

Two authors (CAK and AFC) independently rated the methodological quality of the included systematic reviews and meta-analyses with the Assessment of Multiple

Systematic Reviews (AMSTAR) instrument, which has been validated for this purpose (Pieper et al., 2015; Shea et al., 2007). The scores ranged from 0 to 11 with higher scores indicating greater quality. The AMSTAR tool involves dichotomous scoring (i.e., 0 or 1) of 11 items related to assess the methodological rigor of the systematic reviews and meta-analyses (e.g., comprehensive search strategy and/or publication bias assessment). The AMSTAR scores were graded as high (8-11), medium (4-7), and low quality (0-3) (Shea et al., 2007).

2.4. Statistical analysis

We followed established procedures to assess the epidemiological credibility of possible risk factors for depression (Belbasis et al., 2015; Bellou et al., 2016; Carvalho et al., 2016a). First, for each meta-analysis, we recalculated the summary effect size (ES) with 95% CIs using random-effects modeling (Higgins et al., 2009; Lau et al., 1997) from the individual study data provided in the original meta-analysis. We also estimated the prediction interval (PI) and its 95% CI, which assesses heterogeneity and evaluates the uncertainty of the ES in a new study investigating the same association (Higgins et al., 2009; IntHout et al., 2016). For the largest dataset in each meta-analysis, the standard error (SE) of the effect size was estimated and we examined whether the SE was less than 0.10. In a study with SE < 0.10, the difference between the effect size estimate and the upper or lower 95% CI was less than 0.20, which is regarded as a small effect size (Cohen, 1977).

Between-study heterogeneity was assessed using the I^2 statistic (Patsopoulos et al., 2009). I^2 values may range from 0% to 100% and quantify the variability in the effect size estimates that was due to heterogeneity rather than sampling error (Higgins and Thompson, 2002). Values exceeding 50% and 75% indicated large and very large heterogeneity, respectively.

We also assessed the small-study effects (i.e., whether smaller studies had a tendency to provide more robust effect sizes compared to larger ones) using the Egger's regression asymmetry test (Egger et al., 1997). A $P < 0.10$ combined with a more conservative effect size in the largest study rather than in the summary effect size of the random-effects meta-analysis was judged to provide evidence of the small-study effects (Carvalho et al., 2016b).

We also applied the excess of significance test, which determines whether there is a relative excess of formally significant findings in the published literature due to publication bias, selective reporting of outcomes or analyses, or other reasons. This is a

χ^2 test that assesses whether the observed (O) number of nominally significant findings is larger than their expected (E) number (Ioannidis, and Trikalinos, 2007). We used the effect size of the largest study in each meta-analysis to calculate the power of each study using a non-central *t* distribution (Ioannidis, 2013; Lubin and Gail, 1990). Evidence of excess of significance was claimed when E > O and two-tailed P < 0.10 as previously proposed (Ioannidis and Trikalinos, 2007).

For meta-analyses with type I or II evidence (see below) sensitivity analyses were conducted considering (1) only prospective studies and (2) studies in which depression was diagnosed with a structured or semi-structured diagnostic interview as opposed to studies in which the ascertainment of cases was established through a screening instrument. Data from at least 3 datasets were required to perform these analyses.

Finally, for associations supported by type I or type II evidence, we used credibility ceilings, a sensitivity analysis tool, to account for potential methodological limitations of the included studies (e.g., poor controlling of confounders, recall and interviewer bias, and lack of comparability between the exposed and control groups), which might lead to spurious precision of the combined effect size estimates (Salanti and Ioannidis, 2009). This method assumes that every observational study has a probability *c* (credibility ceiling) that the true effect size is in a different direction from the one indicated by its point estimate. The pooled effect sizes were estimated for a wide range of credibility ceilings (Kyrgiou et al., 2017; Salanti and Ioannidis, 2009).

For the MR studies, we present a descriptive analysis of the eligible studies. If all of the information required for calculation was available (i.e. sample size, number of cases, R^2, estimates of association, and measure of association), we performed a power calculation for the largest MR study using the non-centrality parameter-based approach (Li et al., 2017). Statistical analysis and power calculations were performed using STATA version 12.0.

2.5. Assessment of epidemiologic credibility

The level of epidemiologic credibility for each environmental risk factor was rated in accordance with pre-established criteria: I (convincing evidence), II (highly suggestive evidence), III (suggestive evidence), IV (weak evidence), and NS (all associations had non-significant findings). This set of criteria was used in similar efforts to synthesize evidence of environmental risk factors for other neuropsychiatric disorders (Belbasis et al., 2015; Bellou et al., 2016; Bortolato et al., 2017). In brief, evidence was rated as

convincing evidence when all of the following criteria were met: statistical significance according to random effects models at $P < 10^{-6}$; included more than 1000 cases; lack of large between-study heterogeneity ($I^2 < 50\%$); 95% PI excluding the null value; and no evidence of small-study effects and excess significance. Other associations with more than 1,000 cases, $P < 10^{-6}$, and the largest study presenting a statistically significant effect were graded as highly suggestive evidence. Other associations supported by > 1,000 cases and a significant effect at $P < 10^{-3}$ were rated as suggestive evidence, while all remaining nominally significant associations (at $P < 0.05$) were considered as having weak evidence.

3. Results

3.1. Overall assessment of meta-analyses

Overall, the title and abstracts of 5,869 unique references were evaluated for eligibility (Figure 1), while full texts of 460 references were scrutinized for eligibility. Finally, 382 references were excluded after full-text review with reasons (Supplementary Table S1, available online), leaving 78 unique references that met the eligibility criteria (70 references were meta-analytic reviews and the remaining 8 were MR studies).

Data from 1,283 original studies that assessed 89 different associations of environmental risk factors for depression (Table 1), 6 unique associations with pediatric depression (Table S3, available online), and 39 putative associations with late-life depression (Table 2) were obtained from the 70 meta-analytic reviews. Therefore, 134 different associations of risk factors for depression were identified and examined through meta-analysis. The median number of datasets included in the meta-analyses was 7.5 (IQR: 5-11), and the number of cases was > 1,000 in 56 (41.8%) meta-analyses. The heterogeneity was large ($I^2 > 50\%$) in 76 (56.7%) meta-analyses, while 24 (17.9%) meta-analyses exhibited evidence of small-study effects. Excess of statistical significance could not be calculated for 29 (21.6%) meta-analyses (Chang-Quan et al., 2010a; Chang-Quan et al., 2010b; Grosso et al., 2016; Hasan et al., 2015; Huang et al., 2010; Lorant et al., 2003; Luger et al., 2014; Ttofi et al., 2011; Wang et al., 2016; Xiu-Ying et al., 2012; Yan et al., 2011; Zhai et al., 2015), and this type of bias was observed in 17 (12.7%) meta-analyses (Bonde et al., 2016; Cole and Dendukuri, 2003; Huang et al., 2010; Osborn et al., 2014; Pan et al., 2012; Parsaik et al., 2014; Rahe et al., 2014; Zhao et al., 2012). The overall methodological quality of the included meta-analyses was medium (median AMSTAR score: 6; IQR: 5-7). Table S2 (available online) provides scores for each included meta-analysis.

<Please insert Figure 1 here>

<Please insert Table 1 here>

<Please insert Table 2 here>

3.2. Environmental risk factors for depression

Of 89 associations of environmental risk factors for depression in adults (age ≥ 18 years), 68 (77.3%) were nominally significant (P < 0.05). These associations pertained to dietary factors (number of associations, k = 18), drugs/substances (k = 3), family factors (k = 2), habits/lifestyle factors (k = 6), infections (k = 6); medical history and comorbid diseases (k = 14), obesity and metabolic abnormalities (k = 17), pregnancy and birth-related factors (k = 3), socio-demographic factors (k = 10), and exposure to trauma/disasters (k = 10) (Table 1). Only 8 associations were supported by type I evidence: obesity, exposure to physical abuse in childhood, the presence of 4-5 metabolic risk factors, tea intake, sexual dysfunction, job strain, widowhood, and dietary zinc (Figure 2). However, in a sensitivity analysis in which only prospective studies were considered, obesity, exposure to physical abuse in childhood, the presence of 4-5 metabolic risk factors, sexual dysfunction, job strain, and widowhood remained supported by type I evidence, while the association with tea intake was no longer statistically significant, and only 2 studies found an association with zinc intake (Table S4, available online). In a sensitivity analysis where only studies in which a case definition of depression was established using a structured diagnostic interview as opposed to studies that used screening instruments were considered, only job strain and widowhood remained supported by type I evidence (Table S5, available online), while sexual dysfunction dropped to type II evidence (after the PI crossed the null and evidence of small-study effects emerged). Exposure to physical abuse was now supported by weak evidence after the number of cases dropped to less than 1,000 (Table S5, available online). Fewer than 3 independent studies in which a structured diagnostic interview was used to assess depression were available for obesity (k = 2 studies), the presence of 4-5 metabolic risk factors (k = 2), tea intake (k = 1), and dietary zinc (k = 1). Thus, sensitivity analyses were not performed.

Finally, all environmental risk factors with the exception of job strain survived 10% credibility ceilings, while obesity, exposure to physical abuse in childhood, and the presence of 4-5 metabolic risk factors remained nominally significant when 20% credibility ceilings were considered (Table S6, available online).

<Please insert Figure 2 here>

Furthermore, 9 associations were supported by type II evidence: intimate partner violence against women, co-occurring psoriasis, the metabolic syndrome, the presence of 3 metabolic risk factors, sedentary behavior, being a Gulf War veteran, exposure to sexual abuse during childhood, exposure to emotional abuse during childhood, and dry eye disease with Sjögren's syndrome (Table 1). When only prospective studies were considered, associations with the presence of 3 metabolic risk factors and exposure to physical abuse during childhood remained supported by type II evidence, while associations with exposure to emotional abuse during childhood dropped to type III evidence after the significance level was between 10^{-6} and 10^{-3}, and the association with metabolic syndrome dropped to weak as the significance was higher than 10^{-3} (Table S4, available online). When the sensitivity analysis considered only studies in which a diagnosis of depression was established through a structured diagnostic interview, then associations with being a Gulf War veteran was supported by type I evidence whereas associations with intimate partner violence against women, co-occurring psoriasis, and the presence of 3 metabolic risk factors remained supported by type II evidence (Table S5, available online). Associations with exposure to sexual abuse during childhood dropped to type III evidence, while associations with exposure to emotional abuse during childhood were supported by weak evidence after changes in the significance level (Table S5, available online). In addition, associations with metabolic syndrome were no longer nominally significant, while a sensitivity analysis could not be performed for the presence of 3 metabolic risk factors, sedentary behavior, and the presence of dry eye with Sjögren's syndrome because fewer than 3 independent studies were available (Table S5, available online). Finally, all associations supported by type II evidence remained nominally significant when 10% credibility ceilings were considered (Table S6, available online).

3.3. Environmental risk factors for pediatric depression

Six environmental risk factors for depression in youths have been examined through meta-analyses. The presence of co-occurring asthma was supported by type II evidence (Lu et al., 2012). No sensitivity analysis considering only prospective studies or studies in which depression was assessed using a structured diagnostic interview could be performed for this association because fewer than 3 independent studies were available. Any childhood maltreatment and obesity were supported by type III evidence. The remaining associations, namely smoking and childhood chronic illnesses (cancer or diabetes), were not statistically significant (Table S3, available online). The association

with co-occurring asthma remained nominally significant at 10% credibility ceilings, but was no longer significant at 20% credibility ceilings (Table S6, available online).

3.4. Environmental risk factors for late-life depression

Thirty-nine associations of environmental risk factors for late-life depression were examined across 10 included articles (Table 2) pertaining to dietary factors (k = 2), family factors (k = 1), medical history and comorbid diseases (k = 20), obesity and metabolic factors (k = 2), socio-demographic factors (k = 13), and exposure to trauma and disasters (k = 1). No association was supported by type I evidence, although poor health status, presence of a chronic disease, poor vision, low educational level, and sleep disturbances were supported by type II evidence (Figure 2). However, when only prospective studies were considered, associations with the presence of a chronic disease were then supported by type III evidence, while the association with a low educational level was supported by weak evidence after changes in the significance level (Table S4, available online). Only the association with sleep disturbances remained supported by type II evidence whereas a sensitivity analysis limited to prospective studies could not be conducted for associations with poor health status or poor vision because fewer than 3 component datasets were available (Table S4, available online). Furthermore, when only studies in which a diagnosis of depression was established through a structured diagnostic interview were considered, associations with educational level and poor health status were then supported by weak evidence because the number of cases dropped to less than 1,000, while the association with sleep disturbances was supported by type III evidence after changes in the significance level (Table S5, available online). Furthermore, all associations that were supported by type II evidence remained nominally significant when 20% credibility ceilings were considered (Table S6, available online).

3.5. Mendelian randomization studies

Ten MR analyses were identified from 8 publications (Table 3). The median number of participants was 9,240 (range: 2,404-82,608) and the median number of cases was 2,430 (range: 610-9,519). Six unique environmental risk factors (Table 3) were investigated in individual MR studies: smoking, alcohol consumption, obesity, body mass index (BMI), age of menarche, and coffee consumption. The proportion of variance in risk factors (R^2) explained by genetic instruments was 0.1-0.4%. These small values limit the evidence derived from MR studies. More than one MR study was identified for 2 outcomes (tobacco smoking and alcohol consumption), and four studies used more than

one genetic variable (Table 3). Discordance in either the direction and/or statistical significance of associations among overlapping MR investigations existed for alcohol consumption and smoking. Age of menarche presented significant associations at $P < 0.05$ for one among multiple analyses for only some quartiles (Sequeira et al., 2017). Body mass index association was investigated using several MR methods (Hartwig et al., 2016), but only the weighted median method showed a statistically significant association at the $P = 0.05$ level (OR = 1.40; 95% CI = 1.03-1.90).

4. Discussion

We systematically collected and appraised putative environmental risk factors for depression that have been examined in meta-analyses of observational studies. While this effort identified 134 associations with depression, including 6 specific associations with pediatric depression and 39 associations with late-life depression, only nine associations met the criteria for convincing evidence (significant at the 10^{-6} level by random-effects meta-analysis, more than 1,000 cases, 95% PI not crossing the null, no small-study effects, small heterogeneity, and no excess of significance). These risk factors included obesity (Jokela et al., 2014), the presence of 4-5 metabolic risk factors (Jokela et al., 2014), widowhood (Onrust and Cuijpers, 2006), sexual dysfunction (Atlantis and Sullivan, 2012), tea consumption (Dong et al., 2015), exposure to physical abuse during childhood (Mandelli et al., 2015), job strain (Madsen et al., 2017), dietary zinc intake (Li et al., 2017), and being a Gulf War veteran (Blore et al., 2015). The latter association was supported by convincing evidence only when the analysis was limited to studies in which the case definition of depression was performed through a structured or semi-structured diagnostic interview. Fifteen environmental risk factors were supported by highly suggestive evidence in the main analysis (i.e., the random-effects meta-analysis was significant at the 10^{-6} level, more than 1,000 cases, the confidence interval of the largest study did not cross the null, and at least one of the following was present: large heterogeneity, PI crossing the null, excess of significance, or small-study effects). These included intimate partner violence against women (Beydoun et al., 2012), metabolic syndrome (Pan et al., 2012), being a Gulf War veteran (Blore et al., 2015), the presence of 3 metabolic risk factors (Jokela et al., 2014), sedentary behavior (Zhai et al., 2015), co-occurring psoriasis (Dowlatshahi et al., 2014), exposure to emotional abuse during childhood (Mandelli et al., 2015), exposure to sexual abuse during childhood (Mandelli et al., 2015), and dry eye disease with Sjögren's syndrome (Wan et al., 2016). In addition, co-occurring asthma was supported by type II evidence

as a risk factor for pediatric depression (Lu et al., 2012). Finally, associations with poor health status (Chang-Quan et al., 2010a), the presence of a chronic disease (Chang-Quan et al., 2010a), poor vision (Huang et al., 2010), lower educational attainment (Chang-Quan et al., 2010a), and sleep disturbances (Bao et al., 2017) were supported by highly suggestive evidence as risk factors for late-life depression.

4.1. Associations of environmental risk factors for depression supported by evidence

Despite the substantial number of associations with convincing or highly suggestive evidence in different analyses, very few factors maintained convincing evidence when the data were limited to prospective studies or those with structured diagnostic interviews. Overall, from the 23 associations supported by at least highly suggestive evidence, 15 could not be analyzed in both sensitivity analyses due to the lack of prospective design or studies using structured diagnostic interviews as diagnosis instruments. Only 118 of the 257 studies investigating these associations were prospective. Therefore, many of these associations should be interpreted with caution.

Most of the factors identified with convincing or highly suggestive evidence were stressors. It is speculated that stressors contribute to the emergence of depression by altering the brain circuits, for example in the amygdalae, which are involved in mood regulation (McEwen, 2003). However, it is unclear why some stressors, but not others, exhibited more convincing associations with depression. It is worth noting that exposure to stressors may also contribute to the bidirectional associations between depression and several chronic disease states through the generation of allostatic overload, which results from the chronic exposure to fluctuating or heightened neural or neuroendocrine responses associated with stress exceeding the coping resources of an individual (Fava et al., 2010).

In particular, we found convincing evidence that exposure to physical abuse during childhood was a risk factor for depression (Mandelli et al., 2015). Physical abuse is physical harm perpetrated by a child's caregiver, including hitting, pinching, kicking, biting, burning, poisoning, or suffocating the child. These findings are consistent with the view that during critical periods of brain development, exposure to trauma may permanently influence brain function and response to stressors later in life via several mechanisms (Ignacio et al., 2016; Lopizzo et al., 2015; Post and Weiss, 1998). However, it should be noted that the epidemiological credibility of those findings decreased when sensitivity analyses were limited to studies in which depression was assessed through structured diagnostic interviews. Evidence suggests that the severity of

depression occurs on a continuum ranging from depressive symptoms captured with a validated questionnaire or a structured clinical diagnosis (Cuijpers and Smit, 2004; Prisciandaro and Roberts, 2009). Notwithstanding that structured diagnostic interviews are considered "gold standards" to ascertain a diagnosis of a mental disorder for research purposes, there are also inherent limitations in this approach (Nordgaard et al., 2013). Nevertheless, associations in which the epidemiological robustness of evidence does not survive sensitivity analysis restricted to studies in which the case definition of depression is established through structured diagnostic interviews should be interpreted with caution and may require further elucidation.

Exposure to childhood maltreatment may also have deleterious systemic consequences. It has been argued that exposure to trauma early in life may be associated with several deleterious health outcomes later in life, some of which may be relevant to the emergence of depressive episodes (Nemeroff, 2016). We found highly suggestive evidence that women exposed to intimate partner violence may have a higher risk of developing depression. Notwithstanding variations across cultures that should be acknowledged (Kessler and Bromet, 2013), most research points to a higher prevalence of depression among women. The mechanisms explaining a greater likelihood to develop depression among women appear complex (Kuehner, 2016), but a higher gender-specific exposure to certain stressors may play a role.

We also found convincing evidence that being a Gulf War veteran is associated with an increased risk of depression when studies that used a structured diagnostic interview for depression were considered (k = 4 studies). This is consistent with the diathesis-stress model of depression, which posits that exposure to more extreme stressors confers an elevated risk of depression (Booij et al., 2013). Finally, it is worth noting that depression could be conceived as a "pathoplastic" syndrome (Keller et al., 2007), in which exposure to different types of stressors could shape symptom expression, further contributing to the heterogeneity of the phenotype (Hu et al., 2016; Keller et al., 2007). However, this association was largely driven from cross-sectional studies, and thus prospective research is warranted.

We found evidence that obesity and the presence of 4-5 metabolic risk factors may increase the risk of developing depression (Jokela et al., 2014). Several mechanisms may contribute to this association, including speculated higher peripheral inflammation (de Melo et al., 2017; Kohler et al., 2017; Liu et al., 2014; Mansur et al., 2015). The concept of "metabolic" depression has been proposed, although the

epidemiological evidence remains modest (Liu et al., 2014; Mansur et al., 2015). The association of obesity and metabolic risk factors with depression may simply suggest that both conditions share common environmental risk factors. It is worth noting that this pooled analysis of 8 large-scale cohort studies provided convincing evidence for an association between obesity and depression (Jokela et al., 2014). However, we observed that the association between obesity and depression was supported only by weak evidence when data from a previous meta-analysis of 8 published cohort studies were considered (Luppino et al., 2010). In addition, an included MR study did not provide evidence of a causal association of obesity as a risk factor for depression (Huang et al., 2010), although we could not estimate the statistical power of this study, and another MR study on the association between BMI and depression provided inconsistent results (Hartwig et al., 2016). Two meta-analyses of prospective studies indicated that adherence to either traditional healthy dietary patterns or to a Mediterranean-type diet could prevent the onset of depression (Rahe et al., 2014). However, these associations were supported by weak evidence. Therefore, although several mechanisms may contribute to potential protective effects of a healthy diet for both depression and its associated metabolic comorbidities, including interactions with the microbiome (Slyepchenko et al., 2017), more well-designed studies including randomized controlled trials are warranted.

The evidence that tea consumption and dietary zinc intake may protect against the development of depression should viewed with caution. Several biological mechanisms may at least in part explain the association of tea consumption and depression (Garcia-Blanco et al., 2016). For example, epigallocatechin gallate, a component of green tea, may have antioxidant effects (Han et al., 2014), while certain flavanols derived from green tea were shown to increase hippocampal brain-derived neurotrophic factor (BDNF) and monoamine levels (Stringer et al., 2015). However, this association was not significant in a sensitivity analysis restricted to prospective studies and there were insufficient data assessing the association of zinc with depression in prospective studies. Furthermore, other lifestyle and dietary factors may confound this association as suggested by the authors of the included meta-analysis (Dong et al., 2015). Associations between single nutrients and outcomes in retrospective studies can be notoriously unreliable, even when the published data seem consistent (Schoenfeld and Ioannidis, 2013). Therefore, further prospective studies are warranted to assess this association.

The same caveats exist for the observed association between zinc and depression. Several lines of evidence have suggested an emerging role for zinc in the pathophysiology of depression (Petrilli et al., 2017). For example, peripheral levels of zinc are lower in individuals with MDD compared to healthy controls (Swardfager et al., 2013), while zinc may exert pleiotropic effects including anti-inflammatory effects, modulatory effects on the glutamatergic N-methyl-D-aspartate (NMDA) receptor, and neurotrophic effects, which could be relevant for the pathophysiology of depression (Petrilli et al., 2017). However, a recent meta-analysis found that controlled trials that have tested adjunctive zinc for the treatment of depression have provided mixed results (Sarris et al., 2016). Furthermore, a sensitivity analysis limited to prospective studies could not be performed as only 2 studies were available from the included meta-analysis (Madsen et al., 2017). Therefore, further evidence from prospective studies and controlled trials are needed to provide more consistent causal inferences for this association.

Several putative sociodemographic risk factors for depression have been examined in meta-analyses. We found convincing evidence that widowhood as opposed to all other types of marital status was significantly associated with depression. However, prospective data does not necessarily rule out reverse causation or confounders. For example, it could be argued that depression prevents remarriage. In addition, type II evidence indicated that a lower educational attainment was associated with a higher risk of late-life depression. These findings are broadly consistent with large-scale cross-cultural findings (Kessler and Bromet, 2013). However, there were variations across different countries (Bromet et al., 2011). In addition, a recent large-scale study confirmed that lower educational attainment was associated with depression (Peyrot et al., 2015). Furthermore, this study found no pleiotropic genetic effects mediating this association, thus suggesting that environmental factors are more likely involved.

Convincing evidence also indicates that sexual dysfunction is associated with depression, and this finding survived sensitivity analysis restricted to prospective studies. An accumulating body of evidence has pointed to reciprocal interactions between sexual dysfunction and depression (de Abreu Barata, 2017). Hence, sexual dysfunction may be either a manifestation of depression or a troublesome side effect associated with the use of antidepressant drugs (Carvalho et al., 2016c).

According to the job strain theory, work-related stress result from the additive effects of high job demands and low job control (Karasek et al., 1988). Convincing evidence indicates that job strain is a risk factor for depression, and the same level of evidence remained after sensitivity analysis restricted to either prospective studies or studies in which depression was assessed through structured diagnostic interviews. However, all of the included studies were conducted in Europe and Canada (Madsen et al., 2017), and thus the extent to which those findings apply to other countries (for example, low- and middle-income countries) deserves further investigation. In addition, the studies did not adjust for baseline depressive symptoms or a history of clinical depression, and the definition of job strain varied across studies. Considering that job strain across the included studies was assessed through self-reported instruments, one cannot rule out the possible influence of the participants' affective states on the reporting of work conditions. Furthermore, reverse causality is possible since the evidence suggests that depression is associated with a significant detrimental impact on work productivity (Broadhead et al., 1990; McIntyre et al., 2015; Stewart et al., 2003).

4.2. Assessment of bias in the literature on environmental risk factors for depression

First, our analyses included assessment of several hints of bias, but did not provide definitive proof thereof (Ioannidis et al., 2007; Ioannidis and Trikalinos, 2007). Evidence of high heterogeneity was observed in 56.4% of eligible meta-analyses. There are clear limitations when interpreting Egger's test, which provides an indication of small-study effects in the context of large heterogeneity (Sterne et al., 2011). A high degree of heterogeneity across studies in a meta-analysis may constitute an indication of bias, which may hinder the interpretation of otherwise statistically significant associations. Nevertheless, it is possible that genuine heterogeneity exists across studies. Several lines of evidence indicate that genuine heterogeneity might operate in depression research. First, significant cross-cultural differences have been reported in the prevalence of depression (Bromet et al., 2011; Kessler and Bromet, 2013), which may be partly due to varying levels of exposure to risk factors. For example, large variability of the conditional prevalence of a major depressive episode considering participants who screen positive for depression appeared when data from different countries in the WMH survey were compared (Bromet et al., 2011). In addition, depression is a heterogeneous phenotype with several subtypes (Hasler et al., 2004; Lichtenberg and Belmaker, 2010), and this heterogeneity might have also complicated the search for significant genetic variants for depression (Direk et al., 2016; Flint and

Kendler, 2014). Furthermore, our sensitivity analyses suggest that study design and case definition through a screening tool compared to a structured diagnostic interview could assess the evaluation of some associations. Selective use of different cutoff points may bias accuracy estimates of screening instruments for depression, even if these instruments are regarded as validated measures (Levis et al., 2017), while this limitation is not evident in gold-standard structured diagnostic interviews for depression.

4.3. Strengths and limitations

Some caveats should be considered when interpreting our analyses. First, as previously mentioned, our analyses are not definitive proof of the identified biases. Second, the methodological quality of the meta-analyses varied; they were on average of medium quality. Third, some potential risk factors for depression that have not yet been subjected to meta-analyses might have been missed. These include some risk factors that have been classically related to depression, namely childhood loss of a parent (Bifulco et al., 1987; Harris et al., 1986), poor parenting style (Parker et al., 1997), lack of social support, and social adversity (Bruce, 2002). Furthermore, the absence of a meta-analytic investigation of an environmental factor does not mean that the environmental factor is unimportant, and environmental factors that are more difficult to assess may not yet have sufficient information. Finally, evidence from MR studies that assessed putative environmental risk factors for depression remains largely negative or inconclusive. For example, two MR studies provided no evidence of a causal association of alcohol consumption and depression (Almeida et al., 2014; Wium-Andersen et al., 2015b). Nevertheless, our analyses indicate that both investigations were underpowered. Allowing for these caveats, the main strengths of this work rest on the topical comprehensiveness of the search, the inclusion of a large body of evidence, and the systematic quantitative and qualitative approaches used to rate the quality of the available evidence.

4.4. Implications

Convincing associations with strong effect sizes may aid in the identification of high-risk populations, regardless of whether or not they are causal. Preventive efforts could be targeted to high-risk populations including children exposed to physical abuse, military personnel exposed to combat, recently widowed adults, obese individuals, and people with 4-5 five metabolic risk factors. This perspective is relevant considering recent evidence that suggests that depression can be prevented in youths (Merry et al., 2011), adults (van Zoonen et al., 2014), and the elderly (Cuijpers et al., 2015). In

addition, a better organization and integration of services could enable the early recognition and management of depression in these populations. For example, a better integration of primary health care services and specialized mental health services could potentially aid in the recognition and treatment of depression among high-risk veterans (Ashrafioun et al., 2016). In addition, some evidence indicates that collaborative care interventions could improve outcomes among patients with depression and co-occurring obesity or with several metabolic risk factors (Katon et al., 2010; Panagioti et al., 2016). Moreover, this umbrella review indicates that several possible risk factors deserve proper meta-analytic assessment.

4.5. Conclusion

This umbrella review mapped the status of 134 putative associations of environmental risk factors for depression across the lifespan. The findings show that despite the large number of putative risk factors investigated in the literature, few associations were supported by convincing evidence. Moreover, MR studies, which could provide a more stringent control for potential confounders, and hence, in theory, more robust causal inferences pertaining to environmental risk factors for depression, remain scarce and provided no convincing evidence. The adoption of reporting guidelines (e.g., Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]) (Vandenbroucke et al., 2007) and a pre-registration of protocols of hypothesis-testing observational studies might advance the availability of higher quality evidence in this field (Dal-Re et al., 2014). These efforts may aid in the identification of at-risk populations who could benefit from targeted preventative strategies.

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Conflicts of interest

Authors report no direct competing interests for the present study.

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Figure Legends

Fig. 1. Flowchart of the study selection.

Fig. 2. Forest plot depicting the effect sizes (relative risks or odds ratios) and 95% CIs of the environmental risk factors for depression supported by type I or type II evidence. Only the primary analyses are presented. See the text for sensitivity analyses. The underlined associations were supported by type I or type II evidence in the prospective studies, and the associations in *italics* were supported by type I or type II evidence in the studies using a structured interview for depression diagnosis. #The association of being a Gulf War veteran was supported by type I evidence in studies in which depression was assessed through a structured diagnostic interview. Other highlighted associations were supported by the same type of evidence.

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Table 1. Characteristics, assessment of epidemiological credibility, and methodological quality assessment of the 88 eligible meta-analyses of environmental risk factors for depression

Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Dietary factors											
Anglin, 2013	Vitamin D deficiency (prospective studies)	NA	3	HR	2.22 (1.42-3.47)	$> 10^{-6}$ but $< 10^{-3}$	0.05-92.87	19	No/No	III	9
Anglin, 2013	Vitamin D deficiency	NA	9	OR	1.31 (1.00-1.71)	0.047	0.63-2.73	53	No/No	Weak	9
Rahe, 2014	Western/unhealthy dietary patterns	NA	9	RR	1.18 (0.97-1.43)	0.096	0.68-2.06	62	No/No	NS	5
Liu, 2016	Vegetable intake	NA	7	RR	0.87 (0.77-0.97)	0.014	0.68-1.11	26	Yes/No	Weak	5
Liu, 2016	Fruit intake	NA	8	RR	0.85 (0.77-0.93)	$> 10^{-6}$ but $< 10^{-3}$	0.67-1.07	42	Yes/No	III	5
Grosso, 2016	EPA + DHA intake	NA	4	RR	0.85 (0.70-1.04)	0.123	0.43-1.72	38	No/NE	NS	5
Li, 2016	Dietary magnesium	NA	10	RR	0.83 (0.73-0.95)	0.006	0.59-1.16	68	Yes/NE	Weak	7
Li, 2016	Fish consumption (highest vs lowest)	1113/496	17	RR	0.83 (0.69-1.01)	0.057	0.42-1.63	72	No/Yes	NS	7
Grosso, 2016	Total n-3 PUFA intake	NA	9	RR	0.82 (0.69-0.97)	0.021	0.55-1.22	36	No/NE	Weak	5
Rahe, 2014	Traditional/healthy dietary patterns	NA	17	RR	0.76 (0.68-0.86)	$> 10^{-6}$ but $< 10^{-3}$	0.50-1.17	79	Yes/Yes	III	5
Rahe, 2014	Mediterranean dietary patterns	NA	4	RR	0.76 (0.64-0.91)	0.002	0.39-1.51	57	No/No	Weak	5
Wang, 2016	Coffee intake	NA	4	RR	0.71 (0.52-0.99)	0.044	0.25-2.02	28	No/NE	Weak	4
Dong, 2015	Tea intake	4373/19174	13	RR	0.68 (0.61-0.77)	$< 10^{-6}$	0.49-0.95	42	No/No	I	7

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Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Psaltopoulou, 2013	High adherence to Mediterranean diet	2951/15223	9	OR	0.68 (0.54-0.86)	0.001	0.37-1.26	50	No/No	Weak	7
Li, 2017	Dietary zinc	3708/16133	8	RR	0.65 (0.57-0.75)	$< 10^{-6}$	0.55-0.77	0	No/NE	I	6
Wang, 2016	Caffeine intake	NA	7	RR	0.65 (0.33-1.29)	0.219	0.05-7.75	97	No/NE	NS	4
Li, 2016	Dietary calcium	NA	5	RR	0.64 (0.38-1.08)	0.097	0.12-3.32	61	No/NE	NS	7
Li, 2017	Iron intake	1045/5809	3	RR	0.40 (0.24-0.65)	< 0.001	0.00-87.36	63	No/No	III	6
Drugs/Substances											
Lev-Ran, 2014	Heavy cannabis use	NA	5	OR	1.43 (1.00-2.04)	0.051	0.54-3.75	36	No/No	NS	7
Lev-Ran, 2014	Cannabis use	NA	6	OR	1.17 (0.97-1.41)	0.102	0.73-1.86	37	No/No	NS	7
Parsaik, 2014	Statins use	NA	7	OR	0.68 (0.52-0.89)	0.005	0.33-1.41	55	Yes/Yes	Weak	7
Family factors											
Onrust, 2006	Widowhood (vs any other marital status)	2720/4868	5	RR	5.59 (3.79-8.23)	$< 10^{-6}$	2.09-14.97	30	No/No	I	3
Beydoun, 2012	Intimate partner violence against women	3003/21569	9	RR	2.57 (2.25-2.94)	$< 10^{-6}$	2.18-3.02	0	Yes/No	II	4
Habits/Lifestyle											
Ho, 2014	Internet addiction	857/6842	5	OR	2.77 (2.04-3.75)	$< 10^{-6}$	1.09-7.02	56	No/No	Weak	5
Luger, 2014	Smoking	NA	77	OR	1.68 (1.55-1.82)	$< 10^{-6}$	0.91-3.10	95	Yes/NE	Weak	4
Zeng, 2016	Secondhand smoke exposure	NA	7	OR	1.60 (1.35-1.90)	$< 10^{-6}$	0.94-2.72	90	No/NE	Weak	7
Zhai, 2015	Long sleep duration	NA	5	RR	1.41 (1.04-1.92)	0.026	0.86-2.32	0	No/NE	Weak	7

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Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Zhai, 2015	Sedentary behavior	60526/148346	24	RR	1.25 (1.16-1.35)	$< 10^{-6}$	0.97-1.60	51	No/No	II	7
Zhai, 2015	Short sleep duration	NA	6	RR	1.25 (0.96-1.62)	0.095	0.86-1.81	0	No/NE	NS	7
Infections											
Wang, 2014	Borna disease virus (BDV) infection	205/2654	15	OR	3.25 (1.62-6.54)	$> 10^{-6}$ but $< 10^{-3}$	0.48-21.92	46	No/No	Weak	7
Wang, 2014	Varicella zoster virus	71/164	3	OR	2.10 (1.02-4.33)	0.045	0.02-229.62	0	No/No	Weak	7
Wang, 2014	Epstein-Barr virus	295/178	4	OR	1.98 (1.20-3.28)	0.008	0.66-5.99	0	No/No	Weak	7
Wang, 2014	Herpes simplex virus (HSV-1, HHV-1)	295/178	4	OR	1.98 (1.20-3.28)	0.008	0.66-5.99	0	No/No	Weak	7
Wang, 2014	Cytomegalovirus	100/135	3	OR	1.94 (0.91-4.14)	0.086	0.01-262.27	0	No/No	NS	7
Wang, 2014	Toxoplasma gondii	40/272	3	OR	1.46 (0.62-3.43)	0.381	0.01-367.24	0	No/No	NS	7
Medical history and comorbid diseases											
Wan, 2016	Dry eye disease with Sjogren syndrome	3062/11178	7	OR	4.25 (2.67-6.76)	$< 10^{-6}$	1.02-2.77	72	No/NE	II	3
Dokras, 2011	Polycystic ovary syndrome	522/475	10	OR	4.03 (2.96-5.49)	$< 10^{-6}$	2.80-5.80	0	No/No	Weak	4
Osborn, 2014	Traumatic brain injury	NA	16	OR	3.41 (2.40-4.84)	$< 10^{-6}$	1.28-9.13	50	No/Yes	Weak	3
Fiest, 2013	Epilepsy (current depression)	1632/79762	3	OR	3.12 (1.70-5.73)	$> 10^{-6}$ but $< 10^{-3}$	0.00-6085.29	91	No/No	III	8
Atlantis, 2012	Sexual dysfunction	5488/5683	6	OR	2.71 (1.93-3.79)	$< 10^{-6}$	1.13-6.50	41	No/No	I	8

Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Baglioni, 2011	Insomnia	NA	21	OR	2.60 (1.98-3.42)	$< 10^{-6}$	0.79-8.57	84	Yes/No	III	4
Atlantis, 2013	COPD/chronic lung disease	297031/7128500	4	RR	2.38 (1.47-3.85)	$> 10^{-6}$ but $< 10^{-3}$	0.31-18.45	78	Yes/No	III	6
Wan, 2016	Dry eye disease without Sjogren syndrome	611517/2927706	6	OR	2.24 (1.50-3.34)	< 0.001	0.88-2.41	99	No/No	III	3
Dowlatshahi, 2014	Psoriasis	86945/271291	9	OR	1.64 (1.41-1.90)	$< 10^{-6}$	1.07-2.51	84	No/No	II	6
Gilbody, 2007	Low folate	1769/13446	10	OR	1.54 (1.09-2.20)	0.016	0.59-4.05	50	No/No	Weak	7
Cheungpasitporn, 2015	Hypomagnesaemia	NA	6	RR	1.34 (1.01-1.79)	0.046	0.68-2.64	33	Yes/No	Weak	7
Hasan, 2015	Diabetes	NA	16	RR	1.25 (1.17-1.34)	$< 10^{-6}$	1.03-1.52	59	No/NE	Weak	4
Mitchell, 2013	Long-term cancer survivor (vs. HCs)	NA	13	RR	1.17 (0.95-1.45)	0.142	0.55-2.51	87	No/No	NS	8
Diprose, 2016	Psychogenic nonepileptic seizures (vs. epilepsy)	196/228	7	RR	1.15 (0.85-1.57)	0.365	0.65-2.04	14	No/No	NS	2
Obesity and metabolic abnormalities											
Jokela, 2014	4 or 5 metabolic risk factors	1191/9586	8	OR	2.06 (1.59-2.68)	$< 10^{-6}$	1.19-3.56	24	No/No	I	3
Jokela, 2014	3 metabolic risk factors	3014/9586	8	OR	1.99 (1.60-2.48)	$< 10^{-6}$	1.20-3.30	35	Yes/No	II	3
Luppino, 2010	Obesity (prospective studies)	NA	8	OR	1.55 (1.22-1.98)	$> 10^{-6}$ but $< 10^{-3}$	0.86-2.79	38	No/No	III	7
Pan, 2012	Metabolic syndrome (prospective studies)	2316/27034	9	OR	1.48 (1.17-1.87)	0.001	0.74-2.95	61	No/Yes	Weak	6

Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Jokela, 2014	2 metabolic risk factors	6691/9586	8	OR	1.45 (1.17-1.80)	$> 10^{-6}$ but $< 10^{-3}$	0.83-2.54	51	Yes/No	III	3
Pan, 2012	Metabolic syndrome	20924/132380	27	OR	1.42 (1.28-1.57)	$< 10^{-6}$	0.97-2.07	55	No/No	II	6
Jokela, 2014	Obesity	7673/11413	8	OR	1.35 (1.21-1.50)	$< 10^{-6}$	1.18-1.54	0	No/No	I	3
Jokela, 2014	1 metabolic risk factor	9855/9586	8	OR	1.32 (1.06-1.65)	0.014	0.72-2.42	60	Yes/No	Weak	3
Tong, 2016	Previously diagnosed diabetes vs. normal glucose metabolism	NA	6	RR	1.29 (1.03-1.62)	0.026	0.88-2.41	49	No/NE	Weak	9
Luppino, 2010	Overweight (prospective studies)	NA	7	OR	1.27 (1.07-1.50)	0.007	0.92-1.74	14	No/No	Weak	7
Chen, 2016	Undiagnosed diabetes vs. Normal glucose metabolism	27579/226971	14	OR	1.27 (1.02-1.59)	0.034	0.94-2.56	77	No/Yes	Weak	7
Nouwen, 2010	Type 2 diabetes mellitus	37964/131033	11	OR	1.24 (1.09-1.40)	$> 10^{-6}$ but $< 10^{-3}$	0.86-1.77	68	No/No	III	6
de Wit, 2010	Obesity (community samples)	NA	16	OR	1.21 (0.96-1.52)	0.103	0.47-3.12	95	Yes/No	NS	4
Chen, 2016	Pre-diabetes vs. normal glucose metabolism	63349/194031	19	OR	1.11 (1.03-1.19)	0.009	0.32-1.38	48	No/Yes	Weak	7
Tong, 2016	Newly diagnosed diabetes vs. normal glucose metabolism	NA	6	RR	1.07 (0.74-1.55)	0.726	1.02-2.77	42	No/NE	NS	9
Jokela, 2014	Overweight	11251/11413	8	OR	1.01 (0.91-1.11)	0.880	0.89-1.14	0	No/No	NS	3

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Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Nouwen, 2011	Impaired glucose metabolism	6236/26722	11	OR	0.95 (0.85-1.07)	0.441	0.74-1.23	25	No/No	NS	5
Pregnancy and birth-related											
Loret de Mola, 2014	Low birth weight (≤ 2500 g)	NA	21	OR	1.38 (1.16-1.65)	$> 10^{-6}$ but $< 10^{-3}$	0.89-2.14	24	No/No	III	5
Loret de Mola, 2014	Small for gestacional age	NA	5	OR	1.14 (0.64-2.03)	0.656	0.20-6.36	49	No/No	NS	5
Loret de Mola, 2014	Premature birth	NA	8	OR	1.08 (0.77-1.52)	0.662	0.45-2.57	48	No/No	NS	5
Sociodemographic factors											
Lorant, 2003	Low socioeconomic status	NA	56	OR	1.87 (1.62-2.16)	$< 10^{-6}$	0.73-4.78	87	Yes/NE	Weak	6
Madsen, 2017	Job strain	1909/25552	7	OR	1.77 (1.46-2.13)	$< 10^{-6}$	1.02-14.01	24	No/No	I	7
Kim, 2016	Insecurely employed vs. securely employed	795/3903	6	OR	1.29 (1.06-1.57)	0.010	0.66-2.53	89	No/Yes	Weak	6
Madsen, 2017	Job strain	982/119229	14	HR	1.27 (1.04-1.55)	0.019	0.88-7.32	25	No/Yes	Weak	7
Kisely, 2017	Indigenous vs. other populations	4843/57988	8	OR	1.24 (0.63-2.44)	0.536	0.11-13.60	97	No/NE	NS	8
Kim, 2016	Employed vs. unemployed	40679/1836	13	OR	1.16 (1.09-1.23)	< 0.001	0.96-1.40	69	Yes/Yes	III	6
Tarricone, 2012	Ethnical group (minority vs. predominant)	13569/32646	19	RR	1.15 (1.00-1.33)	0.050	0.65-2.04	86	No/No	NS	4
Richardson, 2015	Neighborhood socioeconomic conditions	NA	10	OR	1.12 (1.01-1.24)	0.029	0.82-1.53	80	No/No	Weak	7
Watanabe, 2016	Overtime work	432/12990	5	RR	1.05 (0.68-1.61)	0.829	0.28-3.95	54	No/No	NS	5

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Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Puthran, 2016	Medical students vs. non-medical students	NA	6	OR	0.96 (0.65-1.43)	0.857	0.25-3.67	85	Yes/NE	NS	7
Trauma and disasters											
Mandelli, 2015	Emotional abuse in childhood	4112/12337	8	OR	2.78 (1.89-4.09)	$< 10^{-6}$	0.74-10.46	91	No/No	II	7
Mandelli, 2015	Neglect in childhood	1668/3620	6	OR	2.75 (1.59-4.74)	$> 10^{-6}$ but $< 10^{-3}$	0.40-19.06	92	Yes/No	III	7
Chen, 2010	Lifetime exposure to sexual abuse	503/2768	11	OR	2.64 (1.92-3.65)	$< 10^{-6}$	1.03-6.77	68	No/No	Weak	9
Mandelli, 2015	Sexual abuse in childhood	4586/13915	14	OR	2.42 (1.94-3.02)	$< 10^{-6}$	1.19-4.94	69	No/No	II	7
Blore, 2015	Gulf-war veterans (vs. non-deployed personnel)	16826/13136	11	OR	2.37 (1.91-2.93)	$< 10^{-6}$	1.20-4.67	76	No/No	II	5
Bonde, 2016	Natural disaster	NA	5	OR	2.14 (1.18-3.89)	0.013	0.23-19.66	94	No/Yes	Weak	8
Bonde, 2016	Terrorist act	NA	6	OR	2.02 (1.38-2.96)	$> 10^{-6}$ but $< 10^{-3}$	0.57-7.16	82	No/No	III	8
Mandelli, 2015	Physical abuse in childhood	3886/12952	10	OR	1.98 (1.68-2.33)	$< 10^{-6}$	1.33-2.94	42	No/No	I	7
Ttofi, 2011	Bullying victimization during school	NA	20	OR	1.74 (1.54-1.97)	$< 10^{-6}$	1.13-2.68	58	No/NE	Weak	5
Bonde, 2016	Military deployment	NA	7	OR	1.66 (1.10-2.49)	0.015	0.38-7.29	99	No/No	Weak	8

Abbreviations: CI = confidence interval; **NA** = not available; **NE** = not evaluated due to lack of datasets or individual study information for power calculations; **EPA =** eicosapentaenoic acid; **DHA** = docosahexaenoic acid; **HSV-1** = herpes simplex virus type I; **HHV-1** = human herpesvirus 1; **COPD** = chronic pulmonary obstructive disease

***Evidence classification: I** = convincing evidence criteria ($P < 10^{-6}$ per random-effects model; over than 1000 cases; no excess of significance bias; no small studies effects; small heterogeneity; prediction interval not including the null); **II** = highly-suggestive evidence criteria (not meeting type I criteria, but having $P < 10^{-6}$ per random-effects model; over than 1000 cases; effect size of the

largest study not crossing the null); **III** = suggestive evidence criteria (not meeting type I or II criteria, but having $P < 10^{-3}$ per random-effects model; over than 1000 cases); **weak** evidence criteria (all other associations with $P < 0.05$ per random-effects model); **NS** = non-significant associations; **NE** = not evaluated due to lack of individual study information

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Table 2. Characteristics, assessment of epidemiological credibility, and methodological quality assessment of 39 eligible meta-analyses of environmental risk factors for late-life depression

Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Dietary factors											
Petridou, 2016	Low B12	NA	8	OR	1.25 (0.97-1.59)	0.080	0.68-2.29	40	No/No	NS	4
Petridou, 2016	Low folate	NA	11	OR	1.21 (0.98-1.49)	0.079	0.71-2.05	37	No/No	NS	4
Family factors											
Yan, 2011	Marital status (widowed, divorced, never married vs. married)	515/539	8	RR	1.36 (1.01-1.84)	0.042	0.51-3.61	81	No/NE	Weak	4
Medical history and comorbid diseases											
Chang-Quan, 2010	Poor health	8630/16552	11	OR	4.08 (3.25-5.12)	$< 10^{-6}$	1.88-8.84	83	No/No	II	4
Bao, 2017	Persistent sleep disturbances	674/1872	4	RR	3.87 (2.45-6.12)	$< 10^{-6}$	0.90-16.61	27	No/Yes	Weak	8
Chang-Quan, 2010	Chronic disease	9090/15321	10	OR	2.59 (1.78-3.76)	$< 10^{-6}$	0.65-10.30	95	No/No	II	4
Cole, 2003	Prior depression	623/3667	3	OR	2.49 (1.55-4.01)	$> 10^{-6}$ but $< 10^{-3}$	0.01-510.34	71	Yes/No	Weak	5
Huang, 2010	Arthritis	2269/6491	6	OR	2.27 (1.35-3.82)	0.002	0.37-13.85	88	No/No	Weak	6
Huang, 2010	Kidney disease	67/1872	3	OR	2.22 (1.31-3.76)	0.003	0.07-67.38	0	No/No	Weak	6
Huang, 2010	Urologic problems	150/1492	3	OR	2.19 (1.52-3.15)	$> 10^{-6}$ but $< 10^{-3}$	0.20-23.32	0	No/No	Weak	6
Huang, 2010	Chronic lung disease	646/2263	4	OR	2.14 (0.97-4.74)	0.060	0.06-78.35	84	No/No	NS	6
Huang, 2010	Gastrointestinal disease	166/2653	4	OR	1.95 (0.80-4.72)	0.140	0.04-84.40	75	No/No	NS	6
Huang, 2010	Poor vision	11066/20976	12	OR	1.94 (1.67-2.25)	$< 10^{-6}$	1.32-2.86	54	No/No	II	6
Bao, 2017	Sleep disturbances	2610/3545	11	RR	1.92 (1.59-2.33)	$< 10^{-6}$	1.39-2.66	10	No/Yes	II	8
Huang, 2010	Stroke	646/5283	9	OR	1.87 (1.33-2.62)	$> 10^{-6}$ but $< 10^{-3}$	0.66-5.31	66	No/No	Weak	6

Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Huang, 2010	Cardiac disease	1911/10134	6	OR	1.81 (1.41-2.31)	$> 10^{-6}$ but $< 10^{-3}$	0.91-3.60	56	No/No	III	6
Huang, 2010	Poor hearing	4448/13319	7	OR	1.71 (1.28-2.27)	$> 10^{-6}$ but $< 10^{-3}$	0.75-3.91	79	No/No	III	6
Chang-Quan, 2010	Chronic disease (prospective studies)	1056/8755	8	RR	1.53 (1.20-1.96)	$> 10^{-6}$ but $< 10^{-3}$	0.72-3.25	68	No/NE	III	4
Agtmaal, 2017	Cerebral microinfarction	NA	4	OR	1.43 (1.22-1.68)	< 0.001	0.98-2.10	2	Yes/NE	Weak	8
Huang, 2010	Hypertension	762/3348	5	OR	1.28 (0.96-1.72)	0.096	0.53-3.08	57	No/No	NS	6
Agtmaal, 2017	White matter hyperintensities	NA	30	OR	1.24 (1.15-1.34)	$< 10^{-6}$	1.39-2.66	67	Yes/NE	Weak	8
Agtmaal, 2017	Cerebral microbleeds	NA	4	OR	1.18 (1.03-1.35)	0.015	0.88-1.58	0	No/NE	Weak	8
Huang, 2010	Cancer survivors	310/2371	5	OR	0.87 (0.61-1.25)	0.463	0.49-1.57	0	No/No	NS	6
Obesity and metabolic factors											
Huang, 2010	Diabetes	1814/6804	9	OR	1.88 (1.31-2.70)	$> 10^{-6}$ but $< 10^{-3}$	0.57-6.25	82	No/Yes	III	6
Huang, 2010	Diabetes (prospective studies)	518/1009	3	RR	1.50 (0.92-2.44)	0.107	0.01-402.35	71	No/NE	NS	6
Sociodemographic factors											
Zhao, 2012	Age > 70 (prospective studies)	442/4980	4	RR	5.92 (0.52-66.86)	0.150	0.00-819558.94	99	No/No	NS	5
Xiu-Ying, 2012	Live in nursing home (prospective studies)	272/1927	3	RR	1.94 (1.18-3.18)	0.009	0.01-362.10	56	No/NE	Weak	5
Cole, 2003	Lower education	619/5759	4	OR	1.79 (1.14-2.80)	0.011	0.27-12.02	73	Yes/Yes	Weak	5
Zhao, 2012	Age > 80	621/8326	3	RR	1.64 (1.36-1.98)	$< 10^{-6}$	0.47-5.67	1	No/No	Weak	5
Zhao, 2012	Age > 65	15017/7004	6	OR	1.63 (1.24-2.16)	$> 10^{-6}$ but $< 10^{-3}$	0.61-4.35	90	No/Yes	III	5
Chang-Quan, 2010	Low educational level	16590/24067	24	OR	1.58 (1.38-1.82)	$< 10^{-6}$	0.89-2.83	74	No/No	II	4
Xiu-Ying, 2012	Living alone	10478/23612	16	OR	1.55 (1.23-1.95)	$> 10^{-6}$ but $< 10^{-3}$	0.64-3.72	76	No/No	III	5

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Reference	Risk factor	Total number of cases/ controls	Number of primary studies	Effect size metric	Random effects summary effect size (95% CI)	P (by random effects)	95% PI	I^2	Small-study effects/ excess statistical significance	Level of evidence*	AMSTAR
Zhao, 2012	Age > 85	4559/19039	12	OR	1.52 (1.20-1.93)	> 10^{-6} but < 10^{-3}	0.68-3.38	73	No/No	III	5
Chang-Quan, 2010	Low educational level (prospective studies)	3957/6374	12	RR	1.49 (1.16-1.91)	0.002	0.64-3.49	75	No/NE	Weak	4
Zhao, 2012	Age > 75	11219/20534	19	OR	1.35 (1.17-1.56)	> 10^{-6} but < 10^{-3}	0.76-2.39	76	No/No	III	5
Xiu-Ying, 2012	Living alone (prospective studies)	591/754	4	RR	1.27 (0.90-1.79)	0.180	0.45-3.59	21	No/NE	NS	5
Zhao, 2012	Age > 70	11875/10650	6	OR	1.22 (0.97-1.52)	0.089	0.56-2.64	87	No/No	NS	5
Cole, 2003	Unmarried	782/6839	5	OR	1.01 (0.83-1.22)	0.950	0.64-1.59	22	No/No	NS	5
Trauma and disasters											
Cole, 2003	Recent bereavement	713/7507	3	OR	3.95 (3.06-5.08)	< 10^{-6}	0.61-25.51	10	No/No	Weak	5

Abbreviations: CI = confidence interval; **NA** = not available; **NE** = not evaluated due to lack of datasets or individual study information for power calculation

* **Evidence classification: I** = convincing evidence criteria ($P < 10^{-6}$ per random-effects model; over than 1000 cases; no excess of significance bias; no small studies effects; small heterogeneity; prediction interval not including the null); **II** = highly-suggestive evidence criteria (not meeting type I criteria, but $P < 10^{-6}$ per random-effects model; over than 1000 cases; effect size of the largest study not crossing the null); **III** = suggestive evidence criteria (not meeting type I or II criteria, but $P < 10^{-3}$ per random-effects model; over than 1000 cases); **weak** evidence criteria (all other associations with $P < 0.05$ per random-effects model); **NS** = non-significant associations; **NE** = not evaluated due to lack of individual study information.

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Table 3. Risk factors for depression reported in Mendelian randomization studies

Risk factor (Reference)	Population	Sample size/ Number of events (Number of studies)*	Genetic instruments (GI)	Variance (R^2) explained by GI (%)	Type of metric	Estimate of effect (95% CI)	P value	Statistical power
Alcohol consumption (Almeida, 2014)	Australia	3873/610 (DS)	*ADH1B* rs1229984	0.11	OR	GA = 0.99 (0.70, 1.40) AA = 1.65 (0.54, 5.08)	0.946	0.05 0.07
Smoking* (Taylor, 2014)	United Kingdom/ Switzerland/ Denmark/ Norway/ USA/ Netherlands/ Canada	82608/9229 (9) (DEP or DS)	*CHRNA5* rs16969968 and *CHRNA3* rs1051730	NA	OR	Never smokers = 1.01 (0.96, 1.06) Former smokers = 1.02 (0.96, 1.08) Current smokers = 1.01 (0.95, 1.07) Ever smokers = 1.02 (0.98, 1.06)	0.788 0.564 0.756 0.346	NA
Obesity (Hung, 2014)	USA/United Kingdom/Europe	3222/2430 (3) (DEP)	*FTO* rs3751812	NA	β	-0.03 (-0.18, 0.13)	0.730	NA
Obesity (Hung, 2014)	USA/United Kingdom/Europe	3222/2430 (3) (DEP)	wGRS from 32 SNPS associated to BMI in GWAS studies	NA	β	-0.02 (-0.11, 0.07)	0.620	NA
Body-mass index (BMI)** (Hartwig, 2016)	USA/United Kingdom/Europe/ Australia	9240/9519 (DEP)	90 BMI-associated SNPs	NA	OR	IVW = 1.15 (0.92, 1.44) Weighted median = 1.40 (1.03, 1.90) MR-Egger = 1.28 (0.74, 2.24) MR-Egger (SIMEX) = 1.33 (0.72, 2.47)	0.221 0.035 0.374 0.364	NA
Body-mass index (BMI)** (Hartwig, 2016)	USA/United Kingdom/Europe/	9240/9519 (DEP)	86 SNPs non-influential on	NA	OR	IVW = 1.25 (1.02, 1.52) Weighted median = 1.45 (1.05, 1.99)	0.030 0.026	NA

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	Australia	BMI***	MR-Egger = 1.52 (0.93, 2.49)	0.094
			MR-Egger (SIMEX) = 1.60 (0.93, 2.75)	0.087

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Age of menarche (continuous genetic instrument) (Sequeira, 2017)	United Kingdom	2404 (DS at 14yo) 2145 (DS at 17 yo) 1570 (DS at 19 yo) 1910 (DEP at 18 yo)	nwGRS from 123 SNPSs associated with menarche in GWAS	NA	OR	1.020 (1.005, 1.04) 1.002 (0.99, 1.02) 1.001 (0.98, 1.02) 1.004 (0.98, 1.03)	0.010 0.780 0.880 0.730	NA NA NA NA
Age of menarche (categorical genetic instrument) (Sequeira, 2017)	United Kingdom	2404 (DS at 14yo) 2145 (DS at 17 yo) 1570 (DS at 19 yo) 1910 (DEP at 18 yo) 	nwGRS from 123 SNPs associated with menarche in GWAS (2nd, 3rd and 4th quartiles vs. 1st quartile)	NA	OR	1.62 (1.18, 2.25) 1.38 (0.99, 1.92) 1.74 (1.26, 2.40) 0.95 (0.71, 1.26) 0.90 (0.68, 1.21) 1.08 (0.82, 1.43) 0.74 (0.52, 1.04) 0.81 (0.58, 1.12) 1.06 (0.76, 1.46) 0.84 (0.55, 1.28) 0.83 (0.54, 1.26) 1.14 (0.76, 1.70)	0.003 0.050 0.001 0.730 0.490 0.590 0.080 0.200 0.740 0.410 0.370 0.530	NA NA NA NA
Tobacco smoking (Wium-Andersen, 2015)	Denmark	40014/771 (CDD)	*CHRNA3* gene cluster rs1051730	0.4	OR	CT = 1.02 (0.88, 1.18) TT = 0.85 (0.66, 1.10)	0.440	0.05 0.06
Alcohol consumption (Wium-Andersen, 2015)	Denmark	78154/1106 (CDD)	*ADH1B* rs1229984 and *ADH1C* rs698 genotype combinations (2 vs. 1, 3 vs. 1,	0.12	OR	1.18 (0.85, 1.63) 1.10 (0.80, 1.53) 1.40 (1.00, 1.96)	0.060	0.05 0.05 0.07

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			4 vs. 1)					
Coffee consumption (Kwok, 2016)	USA/United Kingdom/Europe/ Australia	9240/9519 (DEP)	Genome-wide significant SNPs[#]	NA	OR	0.89 (0.66, 1.21)	0.451	NA
Coffee consumption (Kwok, 2016)	USA/United Kingdom/Europe/ Australia	9240/9519 (DEP)	3 SNPs functionally relevant to coffee metabolism (rs4410790, rs2472297 and rs2470893)	NA	OR	0.95 (0.47, 1.91)	0.886	NA

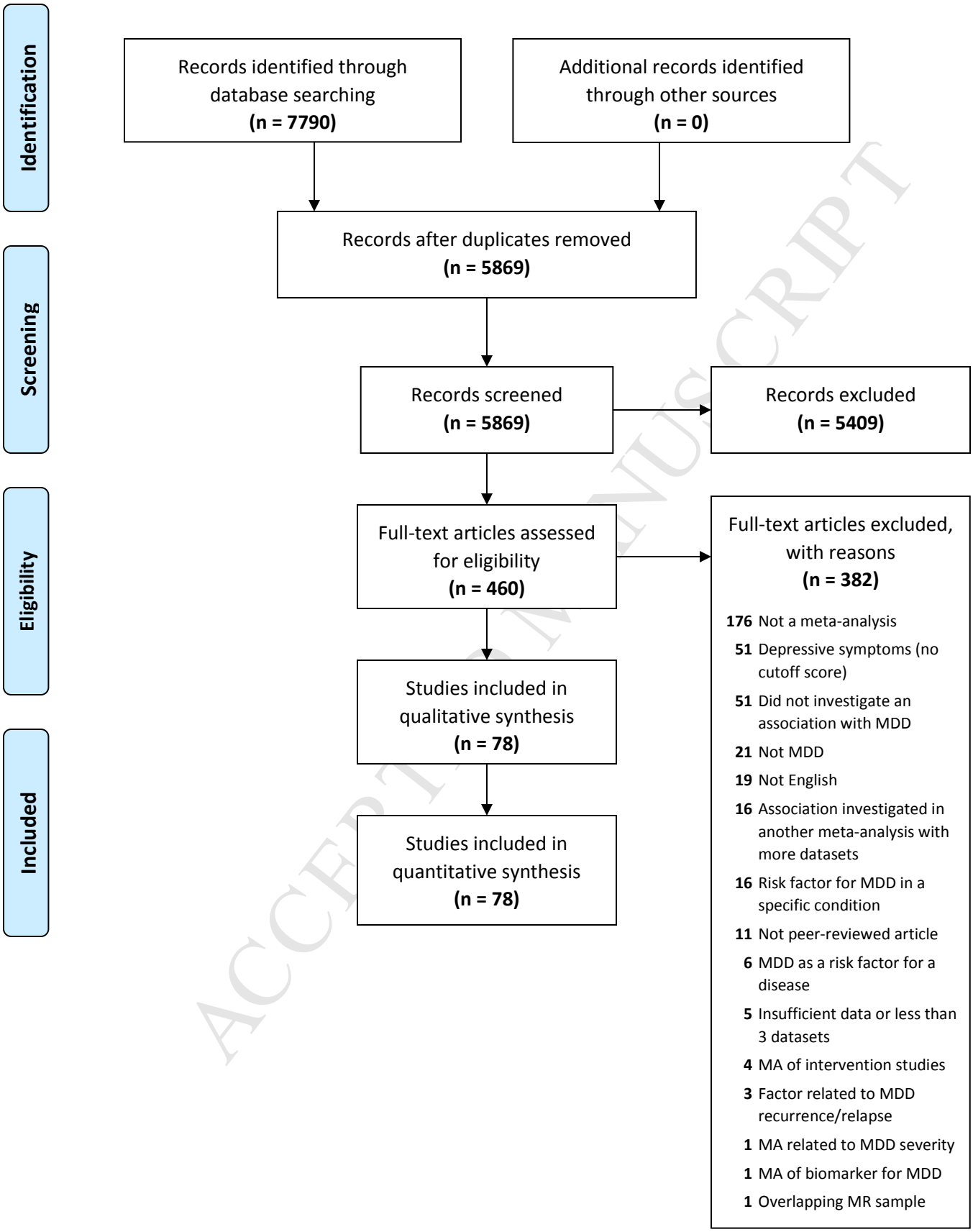
Abbreviations: DS = depression assessed by a screening instrument with a cutoff score; **DEP** = depression diagnosed with structured interview; **CDD** = clinical diagnosis based on ICD criteria for depression; **nwGRS** = non-weighted genetic risk score; **wGRS** = weighted genetic risk score

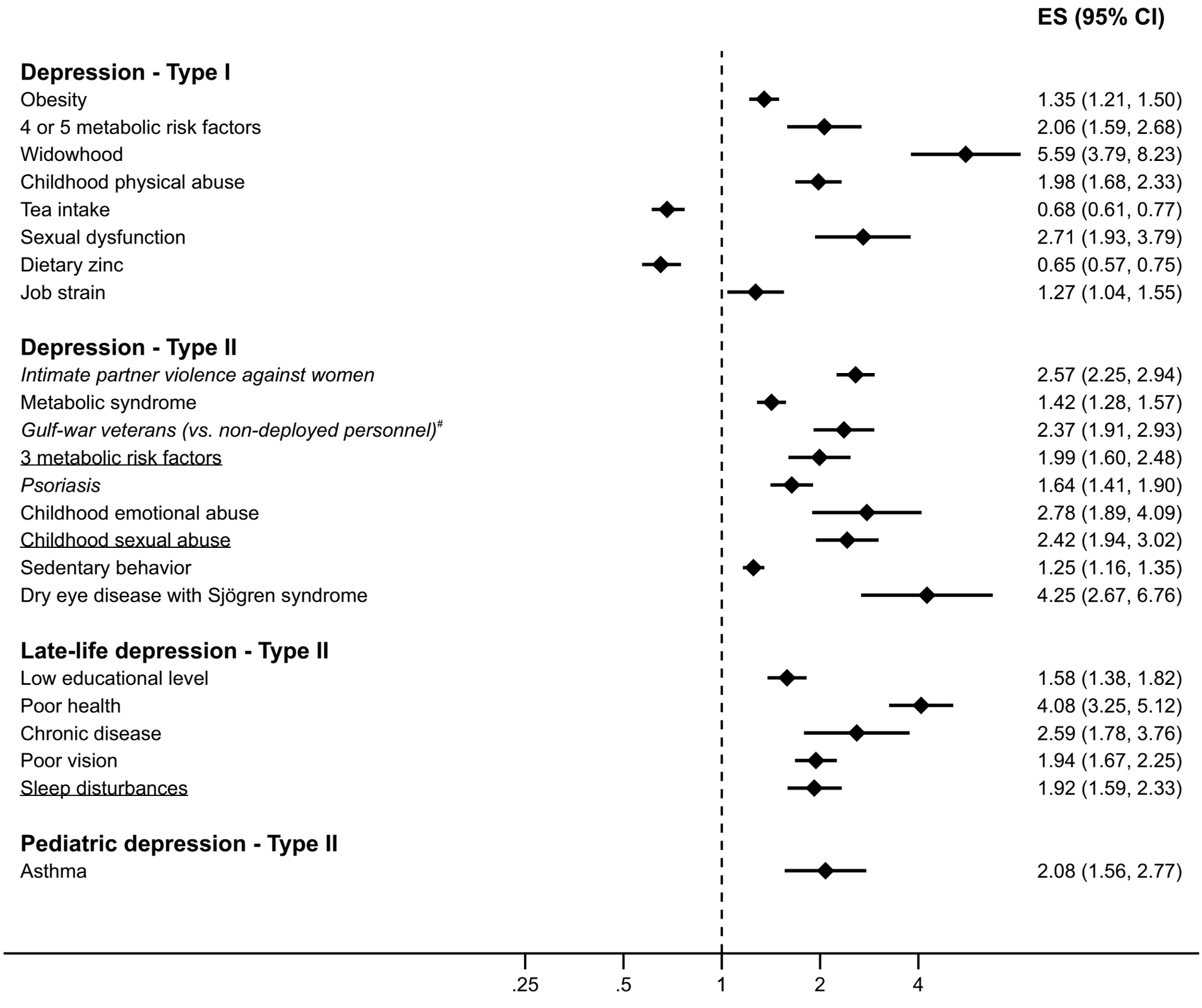
[*]Mendelian randomisation meta-analysis of the studies from the CARTA (Consortium for Causal Analysis Research in Tobacco and Alcohol) consortium. Only datasets 1958 British Cohort, CoLaus, ELSA, Generation Scotland, HBCS, HUNT, NHANES, Rotterdam and SYS-P from the original meta-analysis were eligible according to the depression definition adopted in this umbrella review and were used to recalculate the summary effect size. Summary ORs are presented for each smoking exposure category and were calculated using a fixed-effects model. ORs are expressed per minor allele of the SNP.

[**]This study used three different methods to assess the association of the genetic instrument and depression: inverse variance weighting (IVW), weighted median and MR-Egger regression (with and without simulation extrapolation – SIMEX). The MR-Egger method accounts for violations of instrumental variable assumptions, and the SIMEX procedure corrects for regression dilution. All three methods should provide directionally consistent estimates.

[***]Non-influential SNPs were selected by excluding SNPs that were highly associated in the analysis with all 90 SNPs using tests of influence based on regression residuals.

[#]SNPs included were rs6265, rs17685, rs1260326, rs1481012, rs2470893, rs2472297, rs4410790, rs7800944 and rs9902453; SNPs without known pleiotropy included for analyses were rs17685, rs2470893, rs2472297, rs4410790 and rs9902453.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 7790)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 5869)
Records screened (n = 5869)
Records excluded (n = 5409)
Full-text articles assessed for eligibility (n = 460)
Full-text articles excluded, with reasons (n = 382)
176 Not a meta-analysis
51 Depressive symptoms (no cutoff score)
51 Did not investigate an association with MDD
21 Not MDD
19 Not English
16 Association investigated in another meta-analysis with more datasets
16 Risk factor for MDD in a specific condition
11 Not peer-reviewed article
6 MDD as a risk factor for a disease
5 Insufficient data or less than 3 datasets
4 MA of intervention studies
3 Factor related to MDD recurrence/relapse
1 MA related to MDD severity
1 MA of biomarker for MDD
1 Overlapping MR sample
Studies included in qualitative synthesis (n = 78)
Studies included in quantitative synthesis (n = 78)


ES (95% CI)
Depression - Type I
Obesity
1.35 (1.21, 1.50)
4 or 5 metabolic risk factors
2.06 (1.59, 2.68)
Widowhood
5.59 (3.79, 8.23)
Childhood physical abuse
1.98 (1.68, 2.33)
Tea intake
0.68 (0.61, 0.77)
Sexual dysfunction
2.71 (1.93, 3.79)
Dietary zinc
0.65 (0.57, 0.75)
Job strain
1.27 (1.04, 1.55)
Depression - Type II
Intimate partner violence against women
2.57 (2.25, 2.94)
Metabolic syndrome
1.42 (1.28, 1.57)
Gulf-war veterans (vs. non-deployed personnel)#
2.37 (1.91, 2.93)
3 metabolic risk factors
1.99 (1.60, 2.48)
Psoriasis
1.64 (1.41, 1.90)
Childhood emotional abuse
2.78 (1.89, 4.09)
Childhood sexual abuse
2.42 (1.94, 3.02)
Sedentary behavior
1.25 (1.16, 1.35)
Dry eye disease with Sjögren syndrome
4.25 (2.67, 6.76)
Late-life depression - Type II
Low educational level
1.58 (1.38, 1.82)
Poor health
4.08 (3.25, 5.12)
Chronic disease
2.59 (1.78, 3.76)
Poor vision
1.94 (1.67, 2.25)
Sleep disturbances
1.92 (1.59, 2.33)
Pediatric depression - Type II
Asthma
2.08 (1.56, 2.77)
.25
.5
1
2
4